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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WEHBE, ANNE MARIE SABRINA	
ART UNIT	PAPER NUMBER
1633	

NOTIFICATION DATE	DELIVERY MODE
05/13/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

DocketingDept@young-thompson.com

Office Action Summary	Application No.	Applicant(s)	
	10/585,077	CHRISTENSEN ET AL.	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 February 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *55-57,59-68,70-72,74-88,90-94,102-104 and 109* is/are pending in the application.

4a) Of the above claim(s) *70-72,74-88,90-94,102-104 and 109* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *55-57 and 59-68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/29/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment and response received on 2/1/10 has been entered. Claims 1-54, 58, 69, 73, 89, 95-101, and 105-108 are canceled and new claim 109 has been added. Claims 55-57, 59-68, 70-72, 74-88, 90-94, 102-104, and 109 are currently pending in the instant application.

Applicant's election with traverse of the subject matter of Group I is acknowledged. Applicants traverse the restriction requirement arguing that the inventions are linked by a special technical feature of a homozygous deletion of Serca ATPase. Specifically, the applicant argues that the skilled artisan would have expected that a homozygous deletion of the Serca2 gene would be instantly lethal in adult mice, citing Ver Heyen et al. provided with the instant response, and further that the skilled artisan would not have used a tamoxifen inducible system as claimed because tamoxifen affects cardiac contractility, citing Kargacin et al. and He et al., also provided with the instant response. Applicant's traversal is not found persuasive for the following reasons. First, the independent claims are not limited to a homozygous deletion of the Serca2 gene. In point of fact, the claims as written do not recite any phenotype for the mouse, specify the location of the inserted recombination sites, or even limit the amount of expression of any Serca ATPase gene or slice variant following recombination of the inserted sites. However, in as far as the claims encompass a mouse in which the inserted recombination sites would lead to a deletion of the entire Serca ATPase gene, an embodiment which is not actually claimed in the instant claims, it is noted that while Ver Heyen et al. provides additional evidence that Serca2, and especially the Serca2a isoform are important in cardiac development, where the lack

of Serca2 results in embryonic lethality and even the lack of Serca2a increases embryonic death and the incidence of heart defects, Ver Heyen et al. neither teaches nor suggests that inducing a homozygous disruption of the Serca2 gene in an adult, where the heart is fully developed and functional, would be "instantly lethal". The data shown by Ver Heyen et al. simply suggest that loss of Serca2 gene expression in an adult would negatively affect contraction and relaxation kinetics. In regards to the use of a tamoxifen inducible system, it is noted that of the pending claims, only dependent claim 66 recites the limitation that the mouse comprises a heterologous recombinant system inducible by tamoxifen. Thus, tamoxifen inducible Cre expression is not a technical feature linking the identified inventions. In addition, in regards to unity of invention between Groups I-III, each of these inventions is a separate product, not an "intermediate". Each product is patentably distinct invention, has materially different uses, is made using materially different methods. Further, the products do not share a "special technical feature" required for unity of invention. As such, applicant's arguments have not been found persuasive and the restriction requirement is deemed proper and made FINAL.

Claims 70-72, 74-88, 90-94, 102-104, and 109 are therefore withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 2/1/10. Claims 55-57, 59-68 are currently under examination. An action on the merits follows.

Information Disclosure Statement

The information disclosure statement (IDS) filed 6/29/06 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 for the following reasons: none of the references cited provide the requisite information set forth in 37 CFR 1.98 (b)(5), which states that "Each publication listed in an information disclosure statement must be identified by publisher, author (if any), title, relevant pages of the publication, date, and place of publication". The first two citations are missing page numbers for these publications. The remainder of the citations are missing the name of the publication, i.e. journal, the date of publication, and the relevant page numbers. The IDS has been placed in the application file, but the information referred to therein has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 55-57, 59-68 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic mouse in which both endogenous genomic

copies of the SERCA2 gene contain two loxP sites flanking exons 2 and 3, and whose genome further comprises a MerCreMer transgene under transcriptional control of the α-MHC promoter, and a transgenic mouse model of heart failure wherein said transgenic mouse model is made by administering tamoxifen to a transgenic mouse in which both endogenous genomic copies of the SERCA2 gene contain two loxP sites flanking exons 2 and 3, and whose genome further comprises a MerCreMer transgene under transcriptional control of the α-MHC promoter, wherein the administration of tamoxifen result in the Cre mediated deletion of exons 2 and 3 in both copies of the SERCA2 gene, and wherein the mouse develops heart failure by day 52 following tamoxifen administration, does not reasonably provide enablement for a transgenic mouse in which any genomic Serca ATPase gene has recombination sites inserted in both gene copies . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The specification broadly discloses the use of inserted heterologous recombination sites to induce targeted disruptions in Serca ATPase genes in transgenic mice to generate mouse models for various diseases, and in particular heart disease. The claims as written encompass the insertion of more than one heterologous recombination site into any Serca ATPase gene. It is further noted that while the claims as written encompass various mouse products which are disclosed in the specification as being useful for the production of a mouse model of Serca ATPase related diseases, the claimed mice as set forth in claims 55-57, 59-68 do not actually encompass any mouse model of disease as none of the claimed embodiments of the transgenic mouse recite that the Serca ATPase gene has been disrupted. Thus, the claims under examination

are drawn to intermediate mouse products with no reported phenotype whose sole use is identified in the specification as the production of a mouse model of Serca ATPase related disease.

The specification fails to provide an enabling disclosure for making the breadth of transgenic mice encompassed by the claims, or for using the breadth of transgenic mice encompassed by the claims to produce a mouse model of any disease. In regards to making the breadth of mice encompassed by the claims, while it is acknowledged that the specification provides sufficient disclosure for making a transgenic mouse in which two or more loxP site have been inserted into a Serca ATPase gene (Serca1, Serca2, or Serca3), the specification fails to provide an enabling disclosure for making a transgenic mouse which further comprise a recombinase gene, such as Cre recombinase, that is expressed and active during embryonic and neonatal development. The prior art clearly teaches that the lack of Serca2 during embryogenesis in mice results in an embryonic lethal phenotype such that no Serca2 -/- mice are produced (see Periasamy et al., of record). The prior art also teaches that the lack of Serca1 during embryonic development results in neonatal lethality just hours after birth (Pan et al. (2003) J. Biol. Chem., Vol. 278 (15), 13367-13375). Thus, the prior art clearly establishes that transgenic mice useful as a model of disease cannot be made where the genome of the mouse comprises two loxP or any other recombination sites in a Serca ATPase gene and which further comprises a heterologous nucleic acid encoding a Cre recombinase or any other recombinase where an active form of Cre recombinase is expressed during embryonic development. Further, since neither the prior art nor the instant specification definitively teaches the reasons for early lethality in Serca1 negative and Serca2 negative mice, i.e. which organ(s)or tissue(s) affected by the lack of a Serca ATPase gene

are the cause of death, the skilled artisan would not have been able to predict without undue experimentation whether tissue specific expression of the recombinase in any particular tissue, including heart, could avoid the lethal phenotype associated with a homozygous Serca ATPase deletion during embryonic development.

The specification further does not provide an enabling disclosure for making or using a transgenic mouse which comprises two or more recombination sites in any location of a Serca ATPase gene and which further comprises any inducible Cre recombinase or other recombinase gene. The claims as written read broadly on the placement of the recombination sites anywhere in the Serca ATPase gene such that deletion of the flanked sequence may or may not result in any effect on expression of a functional protein, i.e. the recombination sites could be located within an intron. While the working examples provide specific guidance for the insertion of loxP sites flanking exons 2 and 3 of the Serca2 gene such that recombination of the sites creates a null mutation, the claims are not so limited and encompass the generation of any deletion in the genomic gene sequence. The specification provides no guidance for the enormous number of potential mutations to the genomic gene, or the consequences of any of these mutations on expression of a protein or partial protein product from the mutated gene. The specification further fails to provide any guidance as to the activity or lack thereof of any partial Serca ATPase gene product. Thus, with the exception of the deletion of exons 2 and 3 of the Serca2 gene, the specification fails to provide the requisite guidance for the phenotype of the genus of transgenic mice produced by recombination of the inserted recombination sites as claimed. Note that "case law requires that the disclosure of an application shall inform those skilled in the art how to use

applicant's alleged discovery, not to find out how to use it for themselves." *In re Gardner* 166 USPQ 138 (CCPA) 1970.

In regards to the generation of a null deletion in a Serca ATPase gene, the specification teaches that the embryonic lethal phenotype of a Serca2 negative mouse can be avoided by using an inducible recombinase system such that the timing of deletion of the Serca2 gene can be controlled and delayed until after birth. However, the working examples clearly demonstrate the complexity and unpredictability in choosing an inducible system which is capable of producing a homozygous deletion through recombination of inserted recombination sites. The working example reports a first attempt to generate an inducible Cre and homozygous floxed Serca2 mouse where the inducible Cre system comprises MLC-2v Cre. The working example teaches that Serca2-flox mice, whose genome comprises a homozygous insertion of loxP sites flanking exons 2 and 3 of the Serca2 gene, were crossed with MLC-2v Cre knock-in mice. However, the specification reports that the inventors were in fact unable to generate the expected Serca2 flox/flox MLC2v wt/Cre mouse. Further analysis revealed that linkage between the atap2a2 and myl2 genes on chromosome 5 was 100%, thus preventing generation of the Serca2 flox/flox MLC2v wt/Cre genotype. This example demonstrates that even though the inventors expected to be able to generate the desired genotype, unexpected and unpredictable linkage problems prevented the generation of the desired genotype. However, when the applicant's switched to a different inducible Cre system, where the encoded Cre protein was an inactive Mer-Cre-Mer protein whose activity can be induced by tamoxifen, the applicant's were able to generate Serca2 flox/flox MCM mice. The working example using this mouse further demonstrate knock out of Serca2 following tamoxifen administration to adult mice resulting in the development of heart

failure by day 52. However, for the reasons discussed above and below, this single example of specific mouse genotype which generates a heart failure phenotype useful as a disease model, does not provide enablement for the scope of the instant claims as written.

At the time of filing, the prior art did not consider the phenotype of a knock-out or transgenic mouse to be predictable. In addition, the art did not consider the correlation between any observed mouse phenotypes and human disease phenotypes as predictable. Doetschmann et al. teaches that "[o]ne often hears the comment that genetically engineered mice, especially knockout mice, are not useful because they frequently do not yield the expected phenotype, or they don't seem to have any phenotype" (Doetschmann (1999) Lab. Animal Sci., Vol. 49 (2), 137-143, see page 137, column 1, paragraph 1). Doetschmann provides numerous examples of instances in which genes considered well-characterized *in vitro* have produced unexpected phenotypes or indiscernible or no phenotypes in transgenic or knockout mice. Moens et al. further teaches that different mutations in the same gene can lead to unexpected differences in the phenotype observed. Moens et al. shows that two mutations produced by homologous recombination in two different locations of the N-myc gene produce two different phenotypes in mouse embryonic stem cells, one leaky and one null (Moens et al. (1993) Development, Vol. 199, 485-499). Further, the art demonstrates the unpredictability of making a mouse model for human disease by disrupting the murine gene. Jacks et al. teaches that although retinoblastoma (Rb) gene mutations in humans are associated with retinal tumors, Rb gene knockout mice had tumors in the pituitary gland rather than the retinas (Jacks et al. (1992) Nature, Vol. 359, 295-300). Likewise, whereas HPRT deficiency in humans is associated with Lesch-Nyhan syndrome, a severe neurological disorder, HPRT-deficient mice are phenotypically normal (Kuehn et al.

(1987) Nature, Vol. 326, 295-298 and Jaenisch (1988) Science, Vol. 240, 1468-1474). Thus, the art at the time of filing clearly establishes the unpredictability of determining the phenotype of transgenic or knockout mouse even when the activity of the gene has been extensively studied *in vitro*, and further establishes the unpredictability of generating a mouse model for human disease based on the activity of the gene in humans. It is further noted that specification itself demonstrates the unpredictability in regards to the particular constructs used in the specification to produce a "null" disruption.

Therefore, in view of the art recognized unpredictability in determining the phenotype of transgenic or knockout mouse even when the activity of the gene has been extensively studied *in vitro*, and the unpredictability of generating a mouse model for human disease based on the activity of the gene in humans, the unpredictability in correlating any observed phenotype in a knockout mouse with gene disruption as acknowledged by the prior art, the art recognized problems with early lethality in Serca ATPase knockout mice, the unpredictability in using any inducible recombinase system to generate a homozygous floxed Serca ATPase/ Cre mouse as evidenced by the working examples, the breadth of potential mutations encompassed by the insertion of two or more recombination sites into any location in a Serca ATPase gene, and the general breadth of the claims as written, it would have required undue experimentation to make and use the scope of the instant invention as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 56 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 56 depends on claim 55 and recites the further limitation that the mouse contains several copies of the modified Serca ATPase gene. However, the limitation of claim 56 is confusing as the mouse of claim 55 has a homozygous modification of its genomic Serca ATPase gene where recombination sites have been inserted into the gene. Mice have only two copies of each gene in their genome. Therefore, a homozygous modification of a genomic ATPase gene is limited to a modification of the two genomic copies of the gene. Claim 56 indicates the "several" copies of the modified gene are present the mouse. The term "several" encompasses more than two copies of the gene. As such, the limitation of claim 56 conflicts with the limitation of claim 55 upon which it depends. Thus, the metes and bounds of the claim cannot be determined and claim 56 is indefinite.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 55-57, and 59-68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Periasamy et al. (1999) J. Biol. Chem., Vol. 274(4), 2556-2562, in view of Sohal et al. (2001) Circ. Res., Vol. 89, 20-25.

Periasamy et al. teaches to investigate the function of the SERCA2 gene in heart disease by creating a SERCA2 knockout mouse (Periasamy et al., page 2556). However, Periasamy et al. teaches that mice comprising a homozygous null mutation in the SERCA2 gene exhibit an embryonic lethal phenotype (Periasamy et al., page 2559). Periasamy et al. does teach that mice with a heterozygous mutation in SERCA2, while not exhibiting heart disease, did exhibit changes in calcium uptake and blood pressure (Periasamy et al., pages 2561-2562).

Sohal et al. supplements the teachings of Periasamy et al. by teaching that the embryonic, fetal, or neonatal lethality observed in some homozygous knockout mice which prevents assessment of target gene function in the neonatal or adult heart can be circumvented by the use of an inducible and tissue specific Cre-Lox system (Sohal et al., page 20). Specifically, Sohal et al. teaches methods of making a conditional and tissue specific homozygous knockout mouse comprising a target gene into which two loxP sites have been inserted, and a gene sequence encoding a Cre fusion protein under transcriptional control of a heart specific promoter, where the Cre fusion protein (MerCreMer) is only active in the presence of tamoxifen (Sohal et al.,

pages 20-21). Sohal et al. further demonstrates that the administration of tamoxifen to such a mouse results in heart specific recombination of the loxP sites in the target gene leading to deletion of the target gene sequence bound by the loxP sites (Sohal et al., page 21). Sohal et al. teaches that the MerCreMer system can be used to inactivate any loxP-targeted gene in the heart (Sohal et al., page 23). It is also noted that Sohal et al. teaches that they did not observe any detrimental effects on heart function following tamoxifen administration and that any potential alterations in heart function caused by tamoxifen could be prevented by the use of a lower dose or even a single injection of tamoxifen to induce Cre mediated recombination (Sohal et al., page 24).

Thus, based on the specific teachings and motivation provided by Periasamy et al. for studying the effects of SERCA2 on heart disease by knocking out the SERCA2 gene in a mouse, and the specific teachings of Sohal et al. for avoiding embryonic lethality by using an inducible and heart specific tamoxifen Cre-LoxP system to generate homozygous mutations in a target gene in the heart, it would have been *prima facie* obvious to skilled artisan at the time of filing to use the system described by Sohal et al. to generate a homozygous SERCA2 knockout mouse. Further, based on the successful demonstration by Sohal et al. that the tamoxifen Cre-LoxP system can generate heart specific mutations in a target gene sequence, and the teachings of Periasamy et al. that up to a 55% reduction in SERCA2 protein expression is not lethal to an adult mouse or induce significant heart problems, the skilled artisan would have had a reasonable expectation of success in making a homozygous SERCA2 mouse as claimed.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. If the examiner is not available, the examiner's supervisor, Joseph Woitach, can be reached at (571) 272-0739. For all official communications, the technology center fax number is (571) 273-8300. Please note that all official communications and responses sent by fax must be directed to the technology center fax number. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737. For any inquiry of a general nature, please call (571) 272-0547.

The applicant can also consult the USPTO's Patent Application Information Retrieval system (PAIR) on the internet for patent application status and history information, and for electronic images of applications. For questions or problems related to PAIR, please call the USPTO Patent Electronic Business Center (Patent EBC) toll free at 1-866-217-9197. Representatives are available daily from 6am to midnight (EST). When calling please have your application serial number or patent number available. For all other customer support, please call the USPTO call center (UCC) at 1-800-786-9199.

Dr. A.M.S. Wehbé

/Anne Marie S. Wehbé/
Primary Examiner, A.U. 1633